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Short communication

Epilepsy surgery in drug resistant temporal lobe epilepsy associated with neuronal antibodies

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ABSTRACT

We assessed the outcome of patients with drug resistant epilepsy and neuronal antibodies who underwent epilepsy surgery. Retrospective study, information collected with a questionnaire sent to epilepsy surgery centers. Thirteen patients identified, with antibodies to GAD (8), Ma2 (2), Hu (1), LGI1 (1) or CASPR2 (1). Mean age at seizure onset: 23 years. Five patients had an encephalitic phase. Three had testicular tumors and five had autoimmune diseases. All had drug resistant temporal lobe epilepsy (median: 20 seizures/month). MRI showed unilateral temporal lobe abnormalities (mainly hippocampal sclerosis) in 9 patients, bilateral abnormalities in 3, and was normal in 1. Surgical procedures included anteromesial temporal lobectomy (10 patients), selective amygdalohippocampectomy (1), temporal pole resection (1) and radiofrequency ablation of mesial structures (1). Perivascular lymphocytic infiltrates were seen in 7/12 patients. One year outcome available in all patients, at 3 years in 9. At last visit 5/13 patients (38.5%) (with Ma2, Hu, LGI1, and 2 GAD antibodies) were in Engel's classes I or II. Epilepsy surgery may

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be an option for patients with drug resistant seizures associated with neuronal antibodies. Outcome seems to be worse than that expected in other etiologies, even in the presence of unilateral HS. Intracranial EEG may be required in some patients.

1. Introduction

Autoimmunity is being increasingly recognized as a cause of drug resistant epilepsy. Some patients develop drug resistant seizures after an episode of well-characterized autoimmune encephalitis (Pillai et al., 2016). There is also evidence that autoimmune (paraneoplastic or non-paraneoplastic) limbic encephalitis may present as temporal lobe epilepsy, sometimes associated with hippocampal sclerosis (HS) (Bien et al., 2007; Gaspard, 2016). As neuronal antibody determination becomes more widely available, they are increasingly identified in a subset of patients with chronic epilepsy during the diagnostic workup.

Patients with autoimmune epilepsy usually have high seizure frequency and often display MRI abnormalities, such as HS. In this setting, when antiepileptic and immunosuppressive drugs fail, surgical treatment may be a therapeutic option. The HS observed in these patients probably represents a "burn out" inflammatory process and it is often considered the underlying "structural" cause of the seizures. Less frequently, surgery is performed when the autoimmune etiology has not been suspected yet and the mesial temporal swelling is mistaken for cortical dysplasia or a low-grade tumor (Almeida et al., 2012). The potential role of epilepsy surgery has been only assessed in isolated case reports and small series of patients with neuronal antibodies (Almeida et al., 2012; Kerling et al., 2008; Malter et al., 2015; Muehlebner et al., 2010). The objective of our study was to determine the outcome of a series of patients with epilepsy associated with neuronal antibodies who underwent epilepsy surgery.

2. Methods

This retrospective multicenter study was approved by the Ethics committee of Hospital Clínic, University of Barcelona (Barcelona, Spain). Patients were routinely consented for their clinical information to be included in clinical studies. A questionnaire was sent to 60 tertiary epilepsy surgery centers in Europe, USA, Canada, and Japan to find out if they had any patients who met the inclusion criteria: resective surgery for drug resistant epilepsy and positive neuronal antibodies. We asked about clinical features, acute encephalitic phase if present, immunosuppressive treatment, type and titres of autoantibodies if available, results of presurgical evaluation, pathological findings, and seizure outcome at 1 and 3 years. Surgically treated patients in whom pathological findings were suggestive of chronic encephalitis but no specific antibody was found were excluded from the study. Outcome was assessed by the Engel classification, a widely used tool to categorize the outcome of epilepsy surgery: class I (free of disabling seizures), class II (rare disabling seizures, almost seizure free), class III (worthwhile improvement) and class IV (not worthwhile improvement). Satisfactory outcome included classes I and II.

3. Results

Most epilepsy centers could not provide any patients who met the inclusion criteria. Finally, a total of 13 patients from 8 centers in Europe and the United States were included in the study. Two patients have been previously reported (Almeida et al., 2012; Haberlandt et al., 2011). Mean age at epilepsy onset was 23 years (range: 2–46 years). The following antibodies were detected in serum: GAD (8 patients), Ma2 (2) patients), Hu (1), LGI1 (1), and CASPR2 (1). Antibodies were also detected in CSF in 5/11 patients (CSF not analyzed in 2). Oligoclonal bands in CSF were found in 3 patients. The antibodies were found after surgery in 5 patients (Table 1), most often because of the pathological findings. Eight patients had drug resistant epilepsy without a previous episode of encephalitis (6 GAD, 1 LGI1, 1 CASPR2), whereas the other five patients developed drug resistant epilepsy after a typical episode of autoimmune encephalitis. Associated comorbidities included 3 testicular tumors (2 anti-Ma2, 1 anti-Hu), and several autoimmune disorders, all in patients with GAD antibodies (Table 1). Six patients (five who had encephalitis and one with chronic epilepsy) were treated with immunosuppressive drugs (intravenous corticosteroids ± immunoglobulins). Three patients were still taking maintenance corticosteroids at presurgical evaluation.

Mean time to presurgical evaluation was 9.4 years (range 1–61 years). All patients underwent prolonged video-EEG monitoring with surface electrodes, MRI and neuropsychological testing. No patients underwent monitoring with invasive electrodes. Seizure frequency was daily or monthly (median number: 20 per month, range 2–720). Mean number of antiepileptic drugs was 2.1 (range 1–3). All patients had seizures with temporal lobe semiology. Ten patients had auras, being abdominal (5 patients), and psychic (5) the most common. Four patients displayed multiple types of auras. The most frequently recorded seizures were automotor (with oral or distant hand automatisms and alteration of awareness: 11 patients). Two patients had autonomic seizures (objective piloerection). In addition, four patients had complex motor seizures with irregular movements involving trunk and proximal parts of the limbs and 3 had secondarily generalized tonic-clonic seizures. Interictal surface EEG showed unilateral temporal epileptiform discharges in 9/13 patients, and bilateral temporal discharges in the other 4. Surface ictal EEG showed seizure onset zone in one temporal lobe in 9/13 patients and independently in both temporal lobes in 4/13 patients. Neuropsychological evaluation demonstrated bilateral temporal dysfunction in 4 patients (one with severe anterograde amnesia), unilateral temporal dysfunction in 7 and executive deficits only in 2 patients.

MRI was normal in 1 patient, showed unilateral HS in 6/13 patients, bilateral asymmetric HS in 2/13 patients, unilateral increase in size and signal of mesial structures thought to be a malformation or a low grade tumor in 3/13 patients and bilateral increase in size and signal of mesial temporal structures in 1 patient (Table 1).

Surgical procedures included standard anteromesial temporal resection in 10/13 patients, selective amygdalohippocampectomy in 1, resection of the temporal pole sparing the hippocampus in 1, and stereotactic radiofrequency ablation of mesial structures in 1. Complications after surgery included depression (2 patients), semantic memory deficits (1) and quadrantanopsia (1). Neuropathological findings included lymphocytic infiltrates in 7/12 patients (Fig. 1), along with variable amounts of neuronophagic nodules, microglia activation, neuronal loss, hippocampal sclerosis, and abnormal cortical lamination (Table 1). Seizure outcome was available at 1 year for all patients and at 3 years for 9. At the